Common Drug Review
Clinical Review Report

January 2014

Drug	somatropin (Genotropin) for subcutaneous injection
Indication	The treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed
Listing request	List in similar manner to other growth hormone products
Manufacturer	Pfizer Canada Inc.

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ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AE	adverse event
AUC	area under the concentration curve
AUEC	area under the effective concentration curve
CADTH	Canadian Agency for Drugs and Technologies in Health
CDR	Common Drug Review
CI	confidence interval
Cmax	maximum plasma concentration of drug
CRI	chronic renal insufficiency
ES	estrogen
E. coli	*Escherichia coli*
Emax	maximum effect of drug
FH	final height
GEN	Genotropin
GHD	growth hormone deficiency
h	hour
HCP	host cell proteins
HRQoL	health-related quality of life
Height SDS	height standard deviation score
HV	height velocity
HVSDS	height velocity standard deviation score
IGF-1	insulin-like growth factor-1
im	intramuscular
ISS	idiopathic short stature
IU	international units
kg	kilograms
L	litre
lyo	lyophilized
MA	meta-analysis
max	maximum
mcg	microgram
mg	milligrams
mL	millilitres
NR	not reported
PECP	periplasmic *Escherichia coli* peptides
PWS	Prader-Willi syndrome
QoL	quality of life

RCT	randomized controlled trial
rhGH	recombinant human growth hormone
SAE	serious adverse event
sc	subcutaneous
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
SHOX	short-stature homeobox-containing gene
Soma	somatropin
$T_{1/2}$	drug half-life
Tmax	time to reach maximum concentration of the drug
TS	Turner syndrome
WDAE	withdrawal due to adverse event
WMD	weighted mean difference

EXECUTIVE SUMMARY

Introduction

Turner syndrome (TS) is characterized by the absence of all or part of a normal second sex chromosome in females.[1] Around 50% of patients with TS have sex chromosome abnormalities, while the remaining half have one sex chromosome.[1] Mutations of chromosomes in patients with TS lead to a range of clinical features including, but not limited to, short stature.[2] Adult height of untreated women with TS is approximately 20 cm shorter than that of adult women in the general population, with the average height being around 143 cm.[3] Recombinant human growth hormone (rhGH), also called somatropin, is used to accelerate short-term growth in girls with TS.

Genotropin is one of several somatropin products available in Canada and is indicated for the treatment of short stature associated with TS in patients whose epiphyses are not closed at a dose of 0.33 mg/kg per week, divided into six to seven doses. The objective of this report was to conduct a systematic review of the benefits and harms of Genotropin compared with other available somatropin products for the treatment of short stature associated with TS.

Indication under review
The treatment of short stature associated with Turner syndrome in patients whose epiphyses are not closed
Listing criteria requested by sponsor
List in similar manner to other growth hormone products

Results and Interpretation

Included Studies

No randomized controlled trials (RCTs) were identified comparing Genotropin with other somatropin products. The Common Drug Review (CDR) — in consultation with the clinical expert contracted for the review — identified two key clinical issues to consider in the review of Genotropin: a summary of systematic reviews of the efficacy and/or safety of somatropin in TS, and a comparison of the properties of somatropin products available in Canada.

Systematic Reviews of Efficacy and Safety of Somatropin for TS

CDR identified two systematic reviews assessing the efficacy and safety of somatropin in girls with TS. The Takeda et al. (2010)[4] systematic review included six RCTs, and the Li et al. (2007)[5] systematic review included six RCTs and nine observational studies; three RCTs were common to both systematic reviews. Both systematic reviews concluded that somatropin treatment results in greater and more rapid gains in height compared with no treatment. Results from a single Canadian RCT,[6] which had the longest duration of follow-up of all included RCTs and was included in both the Takeda et al.[4] and Li et al.[5] systematic reviews, reported that girls with TS who received somatropin grew an average of 9.3 cm more than untreated girls after 5.7 years of treatment. In the Li et al.[5] systematic review, results from prospective observational studies were consistent with those of RCTs in showing a significantly higher final height and height standard deviation score (Height SDS) in those who received somatropin when compared with a control group. Only the Li et al.[5] systematic review provided data related to health-related quality of life (HRQoL), noting that HRQoL data were sparse, variable, and inconclusive. Adverse

event (AE) data were also sparsely reported in the studies included in the systematic reviews. Higher rates of AEs were reported by the Canadian RCT[6] in those who received somatropin treatment compared with those who did not, with the most frequently reported AEs, reported in > 20% of patients in either the somatropin or control group, being surgical procedures (50% versus 27%), otitis media (47% versus 27%), and ear disorder (20.3% versus 6.3%), respectively. In addition, significantly higher insulin-like growth factor-1 (IGF-1) concentrations were reported in patients receiving somatropin compared with no treatment. No serious AEs were observed during somatropin treatment in four comparative observational studies.

Comparison of the Properties of Somatropin Products Available in Canada

Of the somatropin products approved by Health Canada, only Humatrope, Nutropin, Saizen, and now Genotropin have a Health Canada indication for treatment of short stature associated with TS. The four products are variable in their concentration and administration formats, with the recommended dose being lower for Genotropin (0.33 mg/kg/week) than for the other three products (0.375 mg/kg/week). In addition, there are differences in the pharmacokinetic profiles of the different products; however, these differences are slight and are not expected to result in important clinical differences. The clinical expert consulted for this review indicated that clinicians consider all somatropin products to be similarly efficacious and safe, with their primary distinguishing features being their formulation (powder versus solution), injection device (syringes versus pens), potential to cause stinging at the injection site, and cost. The clinical expert noted that product selection is generally based upon patient and/or parent preference in consultation with the clinician, and that switching between products is not a frequent occurrence. However, it is noted that because of the difference in the recommended dose between Genotropin and other somatropin products indicated for TS, there is the potential for dosing errors when switching between products.

Pharmacoeconomic Summary

Somatropin (Genotropin) is available as an injection under multiple strengths (0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg syringes, and 5.3 mg and 12 mg pens). The manufacturer used a cost-minimization analysis to support its request for reimbursement of Genotropin for use in patients with TS. Similar clinical effectiveness for Genotropin versus comparators was assumed based on the results of one trial comparing Genotropin with Omnitrope in children with growth hormone deficiency (GHD).[7] There were no published indirect comparisons of these agents. Based on CDR calculations using a confidential price of $[redacted] per mg, the daily cost of the maximum dose of Genotropin ($[redacted]; 0.33 mg/kg/week) is less than that of Humatrope ($100; 0.375 mg/kg/week), Nutropin ($84; 0.375 mg/kg/week), and Saizen ($96; 0.320 to 0.375 mg/kg/week).

Conclusions

Based on the findings of two systematic reviews, it appears that somatropin treatment results in greater and more rapid gains in height, including final height, compared with no treatment. However, whether quality of life is improved in those treated with somatropin compared with those untreated is uncertain. Genotropin is one of several somatropin products approved by Health Canada for the treatment of short stature associated with TS; others include Humatrope, Nutropin, and Saizen. There is insufficient evidence on the comparative efficacy and safety of the somatropin products for the treatment of short stature associated with TS. In clinical practice, product selection is generally based upon patient and/or parent preference, in consultation with the clinician.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Turner syndrome (TS) is characterized by the absence of all or part of a normal second sex chromosome in females.[1] Around 50% of patients with TS have sex chromosome abnormalities, while the remaining half have one sex chromosome.[1] Mutations of chromosomes in patients with TS lead to a range of clinical features including, but not limited to, short stature.[2] Features such as higher risk of scoliosis, skeletal abnormalities, lymphedema, cardiovascular abnormalities, and higher rates of hearing problems and ear malformations can also be present in patients with TS.[2] Adult height of untreated women with TS is approximately 20 cm shorter than that of adult women in the general population, with the average height being around 143 cm.[3] The variation in height among women with TS may be due to age of onset of puberty, the height of both parents, social background, and nutritional status.[5]

Due to the high rate of miscarriage of fetuses with TS, prenatal prevalence of TS is higher than that of postnatal.[8] The reported prevalence of TS among female live births is one in 2,500 to one in 3,000.[1] There were 184,049 female live births in Canada in 2011;[9] hence, each birth cohort has an estimated 62 to 74 cases of TS in Canada, with the estimated number of girls with TS from birth to 12 years old to be between 744 and 888 cases.

1.2 Standards of Therapy

Recombinant human growth hormone (rhGH) treatment is used to accelerate short-term growth in girls with TS. The American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for Growth Hormone Use in Adults and Children recommends the initiation of rhGH treatment in girls with TS as soon as their height is below the fifth percentile of the normal growth curve and states that rhGH therapy may be initiated in girls at two years of age; however, the AACE guideline notes that there is only limited experience available with rhGH treatment in girls that young.[10] In addition, the AACE guideline recommends that therapy can be started with rhGH alone for girls younger than 9 to 12 years of age.[10] The Turner syndrome Consensus Study Group[2] recommends that therapy may be continued until little growth potential remains (growth velocity < 2 cm/year and bone age ≥ 14 year) or until a satisfactory height has been attained. The AACE recommends a starting dosage of rhGH of 0.05 mg/kg per day.[10] Estrogen or oxandrolone are sometimes used with rhGH for the treatment of girls with TS.[11,12] Oxandrolone is recommended by the AACE guideline to be used in addition to rhGH therapy in girls with TS who are older than nine to 12 years of age, or in girls older than eight years of age in whom therapy was initiated when the patient was already far below the fifth percentile of the normal growth curve.[10] The AACE guideline indicates that current data showed that at any age in girls with TS, estrogen has no role in growth promoting.[10] However, TS girls receive estrogen replacement therapy as part of their treatment because most girls with TS will lack pubertal progression and sexual maturation due to missing or abnormal second chromosome, which causes ovarian failure.[4] The dose and timing of the use of estrogen therapy need to reflect the process of normal puberty.[2]

In addition to the treatment of short stature condition, over the long term, multidisciplinary care for multiple problems such as growth, ophthalmologic, cardiovascular, and otologic issues is needed for girls with TS.[5] Moreover, due to the potential for behavioral and social problems, and poor self-esteem in girls with TS, experts increasingly suggest behavioral and educational interventions.[12]

1.3 Drug

Genotropin's active ingredient is rhGH (also called somatropin), which is produced via recombinant DNA technology. The amino acid sequence of Genotropin is identical to that of human growth hormone of pituitary origin, therefore stimulating linear growth in children, tissue growth (skeletal growth and cell growth), protein metabolism, carbohydrate metabolism, lipid metabolism, and mineral and bone marker metabolism and increasing serum insulin-like growth factor-1 (IGF-1).[13] Health Canada has approved Genotropin for the following indications:

- Treatment of short stature associated with TS in patients whose epiphyses are not closed.
- The long-term treatment of children who have growth failure due to growth hormone deficiency (GHD).
- Replacement of endogenous growth hormone in adults with adult onset or childhood onset GHD.
- Treatment of growth failure in short children born small for gestational age (SGA).
- Long-term treatment of idiopathic short stature.

This Common Drug Review (CDR) report is specific to the manufacturer's submission for the indication of TS.

The recommended dose of Genotropin for TS is 0.33 mg/kg of body weight per week divided into six to seven doses and administered by subcutaneous injection.[13] Genotropin is available in numerous dose formulations (0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg syringes, and 5.3 mg and 12 mg pens), intended for subcutaneous injection using one of the following devices: GoQuick pen or MiniQuick syringe.[13]

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List in similar manner to other growth hormone products

The following somatropin products are approved by Health Canada: Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, Norditropin, and Serostim. Of these, Genotropin, Humatrope, Nutropin, and Saizen are indicated for the treatment of short stature associated with TS in Canada.[13-16] Serostim is exclusively indicated for the treatment of HIV wasting associated with catabolism, weight loss, or cachexia. Norditropin is indicated for pediatric GHD and SGA;[17] however, it does not appear to be marketed in Canada currently. Omnitrope is indicated for pediatric and adult GHD.[18] Additional information regarding the indications, dosing, physical characteristics, and pharmacokinetics of the available products may be found in Section Summary of the Properties of Somatropin Products Available in Canada).

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of somatropin, specifically Genotropin, for the treatment of short stature associated with TS.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 1.

TABLE 1: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Female patients diagnosed with short stature associated with Turner syndrome whose epiphyses are not closed
Intervention	SC Genotropin 0.33 mg/kg/week (dosage must be adjusted for the individual patient)
Comparators	• Humatrope • Nutropin • Saizen
Outcomes	**Efficacy outcomes:** • Height (increase in height, final height) • Height velocity • Quality of life **Harms outcomes:** Mortality, AEs, SAEs, WDAEs, harms of special interest (e.g., glucose intolerance, IGF-1 levels, malignancies)
Study Design	Published and unpublished RCTs with a study duration of at least 6 months

AE = adverse event; IGF-1 = insulin-like growth factor-1; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates through Ovid; Embase (1974-) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Genotropin and Turner Syndrome.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See APPENDIX 3: LITERATURE SEARCH STRATEGY for the detailed search strategies.

The initial search was completed on July 22, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on November 20, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), including websites of regulatory agencies, health technology assessment agencies, and clinical guideline repositories. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies. See APPENDIX 3: LITERATURE SEARCH STRATEGY for more information on the grey literature search strategy.

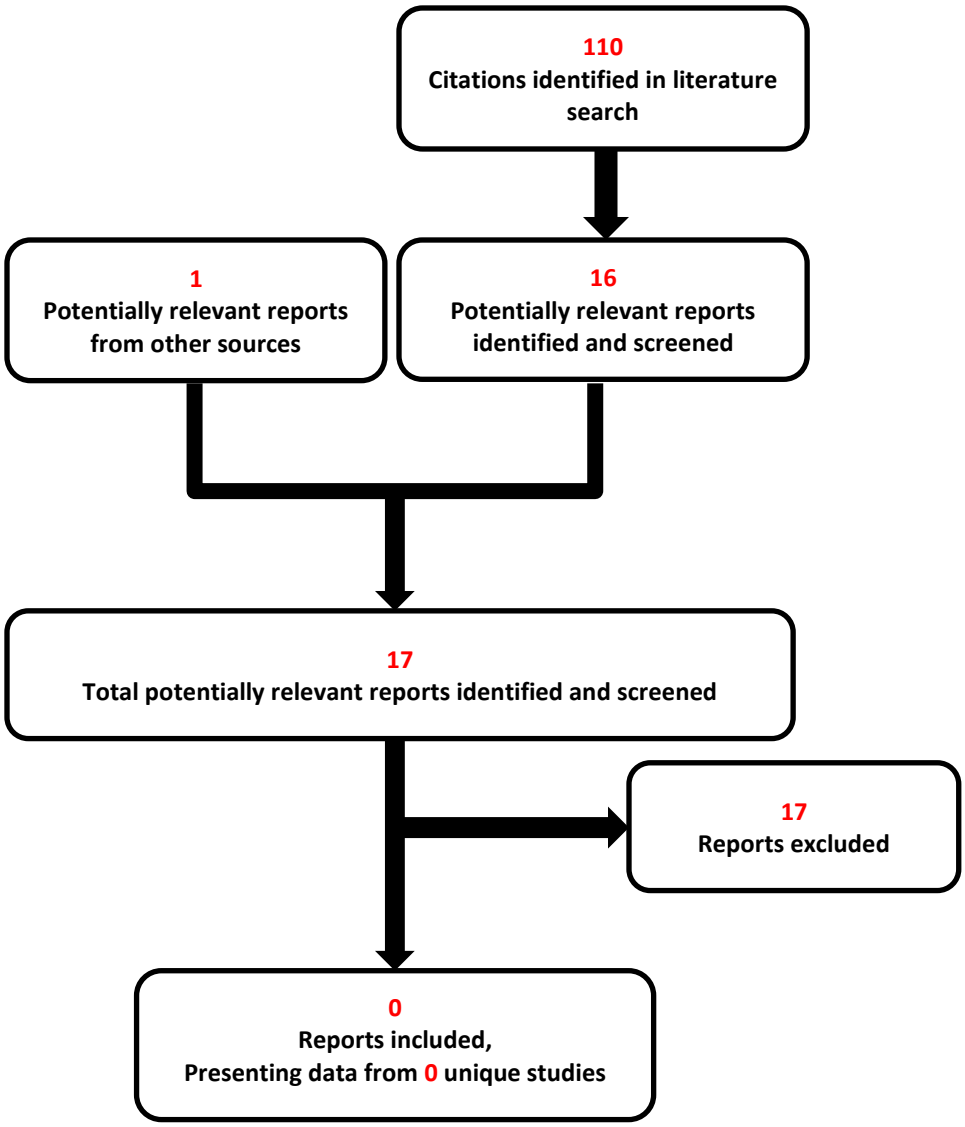
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion. Included studies are presented in Figure 1; excluded studies (with reasons) are presented in APPENDIX 2: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

No studies met the protocol for inclusion in the systematic review. A list of excluded studies is presented in APPENDIX 2: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



3.2 Included Studies

There were no studies that met the protocol for inclusion in the systematic review. Specifically, CDR identified no published or unpublished randomized controlled trials (RCTs) comparing Genotropin with other somatropin products for the treatment of short stature associated with TS.

The manufacturer stated in its submission that there are two randomized, open-label, clinical trials that evaluated the safety and efficacy of Genotropin in patients experiencing growth failure associated with TS; however, those studies compared Genotropin alone with either the combination of Genotropin and low-dose ethinyl estradiol (study TRN 87-055) or the combination of Genotropin and oxandrolone (study TRN 86-092). Thus, these studies were excluded from this review.

Based on the lack of comparative evidence meeting the systematic review protocol, CDR — in consultation with the clinical expert contracted for this review — identified several key clinical issues to consider in the review of Genotropin.

3.3 Key Clinical Issues

3.3.1 Summary of Systematic Reviews of Efficacy and/or Safety of Somatropin for Turner syndrome

A literature search was undertaken to identify systematic reviews of somatropin for TS. Five[4,5,19-21] systematic reviews were identified; however, only two reviews are further described, as they were the most recent reviews and included all studies that were identified in the other three reviews. The two reviews included were a health technology assessment (HTA) report by Takeda et al.[4] and a Canadian Agency for Drugs and Technologies in Health (CADTH) report by Li et al.[5] Takeda et al.[4] (published in 2010) included published RCTs that compared somatropin with no treatment (with no restriction on size of study population, study design, or length of treatment) in children diagnosed with any of the following: GHD, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, short-stature homeobox-containing gene, and SGA. However, further description of this systematic review is limited to the indication of TS. The systematic review by Li et al.[5] was published in 2007 and included both RCTs and comparative observational studies that compared somatropin with placebo or with no treatment (with at least 20 patients and at least one year of treatment with somatropin) in females with TS. Inclusion criteria for the Takeda et al. review[4] and the Li et al. review[5] are summarized in Table 2.

TABLE 2: SUMMARY OF SYSTEMATIC REVIEWS

Author, Year, Study Design	Key Inclusion Criteria	Interventions	Outcomes
Takeda et al. 2010[4] SR	RCTs of patients diagnosed with TS, GHD, SHOX, PWS, CRI, and SGA	Somatropin vs. no somatropin	FH gained, Height SDS, HV, HVSDS, body composition, biochemical markers, AE, HRQoL
Li et al. 2007[5] SR/MA	RCTs or comparative observational studies of patients diagnosed with TS with at least 20 patients and at least 1 year of treatment with somatropin	Somatropin vs. placebo or no treatment	FH, interim height, HV, QoL, AE

AE = adverse event; CRI = chronic renal insufficiency; FH = final height; GHD = growth hormone deficiency; HRQoL = health-related quality of life; Height SDS = height standard deviation score; HV = height velocity; HVSDS = height velocity standard deviation score; MA = meta-analysis; PWS = Prader-Willi syndrome; QoL = quality of life; RCTs = randomized controlled trials; SGA = small for gestational age; SHOX = short-stature homeobox-containing gene; SDS = standard deviation score; SR = systematic review; TS = Turner syndrome.
Source: Takeda et al.;[4] Li et al.[5]

a) Critical appraisal of the systematic reviews

The methodological quality of the included systematic reviews and meta-analyses was evaluated using the AMSTAR instrument, a measurement tool to assess systematic reviews.[22] Acceptable methods to identify, extract, appraise, and summarize studies were used in the Takeda et al. review[4] and the Li et al. review.[5] In the Takeda et al. review,[4] multiple databases were searched, including MEDLINE and Embase via Ovid. Study selection was undertaken by two reviewers, while data extraction and quality assessment (using the National Health Service Centre for Reviews and Dissemination criteria[23]) were undertaken by one reviewer and checked by a second reviewer. Disagreements were resolved through discussion, and narrative review was used to summarize the results from included studies.

In the Li et al. review,[5] multiple databases were searched. Two reviewers independently undertook the study selection. Data extraction and quality assessment (using a scale that combined the Jadad scale[24] and Hailey scale[25]) disagreements were resolved by consensus. Cochrane software Review Manager 4.2.3 was used to analyze data and generate Forest plots; summary estimates were computed wherever possible using the fixed effects and random effects models, and outcomes with continuous data were pooled using weighted mean difference (WMD).

Limitations of the two systematic reviews included the restriction to English language publication only,[4,5] not assessing publication bias,[4,5] not providing a list of excluded studies,[5] and not stating conflict of interest.[4] The critical appraisal is summarized in Table 3 below.

TABLE 3: CRITICAL APPRAISAL OF SYSTEMATIC REVIEWS

Author, Year, Study Design	Strengths	Limitations
Takeda et al. 2010[4] SR	• Literature search of multiple databases including MEDLINE and Embase through Ovid to June 2009. • Robust methods used to select studies, and for quality assessment and data extraction, where one reviewer undertook these tasks and then a second reviewer checked them.	• English language only • Publication bias was not assessed • Conflict of interest was not stated
Li et al. 2007[5] SR/MA	• Literature search of multiple databases including MEDLINE and Embase through Ovid to January 2007. • Robust methods used to select studies, and for quality assessment, data extraction, (where two reviewers independently undertook these tasks) and data synthesis using Cochrane software Review Manager.	• English language only • List of excluded studies was not provided • Publication bias was not assessed

MA = meta-analysis; SR = systematic review.

b) Summary of studies included in the systematic reviews

Takeda et al.[4] included six RCTs, while Li et al.[5] included six RCTs and nine observational studies. Three RCTs (Stephure and the Canadian Growth Hormone Advisory Committee (CGHAC)[6], Quigley et al.[3], and Johnston et al.[26]) were included in both systematic reviews. Takeda et al.[4] was conducted more recently and includes three RCTs that were not included in Li et al.[5], whereas Li et al.[5] included three RCTs and nine observational studies that were not included in Takeda et al.[4] Characteristics of studies included in the Takeda et al.[4] review and the Li et al.[5] review are presented in Table 4.

TABLE 4: KEY CHARACTERISTICS OF STUDIES IN THE TAKEDA AND LI SYSTEMATIC REVIEWS

Included Study	Treatment Duration	Interventions and Comparators	Included in Li et al. 2007	Included in Takeda et al. 2010
RCTs				
Stephure and CGHAC 2005[6a]	5.7 ± 1.6 years (addendum follow-up to 10.6 ± 1.7 years after randomization)	Humatrope 0.30 mg/kg/week (n = 61) vs. no treatment (n = 43)	X	X
Quigley et al. 2002[3]	≥ 1.5 years	Humatrope 0.27 mg/kg/week (n = 45) vs. Humatrope 0.36 mg/kg/week (n = 49) vs. placebo (n = 41)	X	X
Davenport et al. 2007[27]	2 years	Humatrope 50 mcg/kg/day (n = 41) vs. no treatment (n = 37)		X
Gravholt et al. 2002[28]	2 months	Norditropin 0.1 IU/kg/day vs. placebo, n = 12 (crossover RCT)		X
Gravholt et al. 2005[29]	2 months	Norditropin (1.3 ± 0.3) mg/day vs. placebo, n = 9 (crossover RCT)		X
Johnston et al. 2001[26]	> 5 years (duration of randomized treatment: 1 year)	GEN 28 to 30 IU/m^2/week (n = 22) vs. (GEN+ES, n = 23) vs. (ES 50 to 75 ng/kg/day, n = 13) (1 year later, all patients receiving ES received ES+GEN; after 2 years, all patients aged 12 years and older received GEN+ES)	X	X
Kollmann et al. 1991[30]	1 year	Soma 2 IU/m^2/day (n = 29) vs. Soma 3 IU/m^2/day (n = 26) vs. no Soma (n = 29)	X	
Rosenfeld 1990[31]; Rosenfeld et al. 1987[32]	1 year (after 1 year, control group was given active treatment also)	Soma (n = 17) vs. (Soma+OX, n = 17) vs. (OX alone, n = 18) vs. (no Soma or OX, n = 18) Soma = 0.125/kg 3 times a week	X	
Ross et al. 1997[33]	1 to 7 years	Humatrope 0.1 mg/kg 3 times a week (n = 20) vs. placebo (n = 20)	X	
Observational studies				
Bakalov et al. 2004[34]	5.0 ± 2.1 years	Soma (n = 23) vs. no Soma (n = 23), details NR	X	
Bechtold et al. 2006[35]	5.2 ± 2.5 years	Soma (n = 65) vs. no Soma (n = 12), details NR	X	
Bertelloni et al. 2000[36]	5.3 ± 1.4 years	(Soma+ES, n = 14) vs. ES (n = 12), Soma = 0.8 to 1.0 IU/kg/week	X	

Included Study	Treatment Duration	Interventions and Comparators	Included in Li et al. 2007	Included in Takeda et al. 2010
Dacou-Voutetakis et al. 1998[37]	2.2 ± 1.2 years	Soma (n = 82) vs. no Soma (n = 41) Soma = 0.78 ± 0.12 IU/kg/week	X	
Hochberg and Zadik 1999[38]	5.1 ± 1.9 years	(Soma+ES, n = 25) vs. estrogen (n = 24), details NR	X	
Naeraa et al. 1994[39]	Data reported for 2 years	(Soma+ES, n = 18) vs. ES (n = 8) vs. Soma Soma = 0.1 IU/kg/day	X	
Pasquino et al. 1996[40]	3 to 6 years	Soma (n = 18) vs. no Soma (n = 18), Soma = 0.5 IU/kg/week	X	
Pasquino et al. 2005[41]	8.2 ± 1.4 years for patients < 11 years; 5.3±1.6 years for patients > 11 years	Soma (n = 60) vs. no Soma (n = 59), Soma = 0.33 mg/kg/week	X	
Taback et al. 1996[42]	NR	Soma (n = 17) vs. no Soma (n = 14), Soma = 0.05 mg/kg/day 6 days a week	X	

CGHAC = Canadian Growth Hormone Advisory Committee; ES = estrogen; GEN = Genotropin; IU = international units; n = number of patients; NR = not reported; OX = oxandrolone; Soma = somatropin.
[a]Stephure and CGHAC, 2005[6] was the main article; however, Stephure et al. 1993,[43] Rovet and Holland 1993,[44] and Taback and Van Vliet 2011[45] were related articles.

Takeda et al. 2010

The Takeda et al. systematic review[4] included six RCTs,[3,6,26-29] two of which were of a crossover design.[28,29] One RCT was conducted in Canada,[6] two in the US,[3,27] two in Denmark,[28,29] and one in the UK.[26] Four RCTs[3,6,26,27] were multi-centre trials. The age of patients at baseline was broadly similar in five RCTs,[3,6,26,28,29] with mean age ranging between 9 and 15.9 years, while the sixth study[27] included much younger patients with a mean age of around 1.98 years. Bone age was reported in four RCTs[3,6,26,27] and ranged between 1.95 and 8.8 years. Baseline height was reported in five studies[3,6,26,27,29] and ranged from 77.6 cm to 148.3 cm. Different doses of somatropin were used in each RCT, with doses being somewhat lower than that recommended by Health Canada in five of the included RCTs,[3,6,27-29] while the dose used in Johnston et al.[26] ranged between 28 IU/m^2/week and 30 IU/m^2/week, which is approximately equal to between 0.3 mg/kg/week and 0.35 mg/kg/week,[11,46] which includes the recommended dosage by Health Canada.

Takeda et al.[4] considered the included studies to be poorly reported and of poor methodological quality, based on their assessment employing the National Health Service Centre for Reviews and Dissemination criteria.[23] Only one RCT reported an adequate method of randomization, one reported randomization that was judged to be inadequate, and four trials did not describe the randomization technique used. Concealment of treatment allocation was not reported in five trials, and was adequate in one trial. Blinding was judged to be unknown, inadequate, or partial in five trials, and blinding was adequate in one trial. Intention-to-treat analysis was not used in any of the included studies.

No data synthesis using meta-analysis was undertaken because data were of insufficient quality and homogeneity; hence, data from the included studies were synthesized through a narrative review with tabulation of results.

Li et al. 2007

The Li et al. systematic review[5] included 15 studies, including six RCTs[3,6,26,30,31,33] and nine comparative observational studies.[34-42] Of the RCTs in this review, three[3,6,26] were included in the Takeda et al. review.[4] Of the RCTs included, one RCT was conducted in Canada,[6] three in the US,[3,31,33] one in Germany,[30] and one in the UK.[26] One of the studies did not mention the number of centres,[33] while the other five RCTs[3,6,26,30,31] were multi-centre trials. Among the RCTs, the mean age of patients at baseline was broadly similar, ranging between 8.9 and 10.9 years of age. Baseline height and bone age were reported in five RCTs[3,6,26,30,32] and ranged from 114 cm to 122 cm and 7.2 to 8.9 years respectively. Similar to studies included in the Takeda et al. review,[4] different doses of somatropin were used in each RCT, with doses being somewhat lower than that recommended by Health Canada in three of the included RCTs,[3,6,33] and the dose used in Kollmann et al. 1991[30] being much lower than the Health Canada-recommended dose. Rosenfeld et al. 1987 and Johnston 2001 employed doses consistent with those recommended by Health Canada.

A combination scale based on the scales of Jadad et al.[24] and Hailey et al.[25] was used to assess the reporting quality of the included RCTs. Two RCTs[3,6] were found to be of high quality (high degree of confidence in study findings), three RCTs[26,30,31] of good quality (some uncertainty concerning the study findings), and one RCT[33] of fair quality (some limitations). Methods used to assess the quality of included studies in the Li et al. review[5] were different from the method used in the Takeda et al. review,[4] in the sense that more weight or importance was given to the study performance than study design, while the Takeda et al. review[4] was more rigorous in assessing the quality of the studies, considering the methodology, reporting, and study design to be the most important factors to assess; hence, the different conclusion regarding the quality of studies included in both reviews was made.

Of the observational studies included, one study was conducted in Canada,[42] one in the US,[34] three in Italy,[36,40,41] one in Germany,[35] one in Denmark and Iceland,[39] one in Greece,[37] and one in Israel.[38] Five[34-37,42] of the studies were retrospective, while the other four[38-41] were prospective studies. The brand names of the somatropin products used in the observational studies were not specified. The mean age of patients ranged between 10.2 and 21.7 years. Bone age was reported in three studies[37,38,40] and ranged from 9.7 to 11.6. Somatropin dose was reported for six of the nine observational studies,[36,37,39-42] with doses being similar to or slightly lower than Health Canada recommendations.

A combination scale based on the scales of Jadad et al.[24] and Hailey et al.[25] was used to assess the reporting quality of the included comparative observational studies. One study[38] was found to be of good quality (some uncertainty concerning the study findings), six studies[34,37,39-42] of fair quality (some limitations), and two studies[35,36] of poor quality (substantial limitations; findings should be used cautiously).

Data synthesis using meta-analysis was conducted with included RCTs and observational studies in the Li et al. review[5] when sufficient data were reported, and data were found to be homogenous.

As noted in Table 4, the systematic reviews by Takeda et al.[4] and Li et al.[5] included some duplication of evidence (three RCTs), with both Takeda et al.[4] and Li et al.[5] providing a narrative review of the findings of individual studies and with some pooling of studies by Li et al.[5] Thus, to avoid duplication, the following sections integrate results from both systematic reviews.

c) Summary of growth outcomes reported in the systematic reviews

Growth outcomes were reported in four of the six included studies in the Takeda et al. review,[4] where three of the included studies reported height,[6,26,27] two reported change in height and height standard deviation score (Height SDS),[6,27] two reported change in Height SDS,[6,26] three reported height velocity (HV),[3,6,27] and two reported height velocity standard deviation score (HVSDS).[6,27] The Li et al. review[5] reported growth outcomes from five of the six included RCTs and seven of the nine observational studies, where two RCTs[26,30] reported change in Height SDS, three RCTs[3,6,31] reported HV, two RCTs[6,31] reported HVSDS, six observational studies[35-38,40,41] reported final height, and four observational studies reported Height SDS.[36,37,40,41] Results are shown in tables.

Height and Change in Height

Two trials, one by Stephure and CGHAC[6] and one by Johnston et al.[26] had the longest treatment duration. Both studies had a similar starting demographic, with mean ages of 9.1 years versus 10.3 years and mean heights of 114.0 cm versus 119.1 cm for patients included in Johnston et al.[26] and Stephure and CGHAC[6] respectively. The near final height after 5.6 years and 5.7 years of treatment was similar in the two studies, with 146.2 cm and 147.5 cm for Genotropin and Humatrope respectively. Davenport et al.[27] reported height after two years of treatment. Statistically significant differences in mean change in height from baseline between somatropin and no treatment were reported in both the Stephure and CGHAC study[6] and the Davenport et al.[27] study. The between-group differences ranged from 6.8 cm to 9.3 cm for a follow-up period of two years and 5.7 years after randomization respectively. Results are shown in Table 5.

TABLE 5: HEIGHT AND CHANGE IN HEIGHT FROM BASELINE IN THE TAKEDA AND LI REVIEWS

Study	Outcomes	Somatropin (mean ± SD or range)	Control (mean ± SD or range)	*P* Value
Stephure et al. 1993[43]; Stephure and CGHAC 2005[6] (5.7 ± 1.6 years since randomization)	Baseline height (cm)	119.1 ± 8.5	122.0 ± 7.8	NS
	Height (cm) after 5.7 years of treatment	147.5 ± 6.1 (HUM)	141.0 ± 5.4	< 0.001
	Change in height (cm) from baseline after 5.7 years	28.3 ± 8.9	19.0 ± 6.1	< 0.001
Stephure and CGHAC 2005[6] (10.6 ± 1.7 years since randomization)	Baseline height	119.1 ± 8.5	122.0 ± 7.8	NS
	Height (cm) after 10.6 years since randomization	149.0 ± 6.4 (HUM)	142.2 ± 6.6	< 0.001
	Change in height (cm) from baseline after 10.6 years	30.3 ± 8.3	21.6 ± 6.2	< 0.001
Davenport et al. 2007[27]	Baseline height (cm)	78.9 ± 8.6	77.6 ± 8.7	NR
	Height (cm) after 2 years of treatment	99.5 ± 7.6 (HUM)	91.9 ± 7.2	< 0.0001
	Change in height (cm) from baseline after 2 years	20.4 ± 3.3	13.6 ± 3.5	< 0.001
Johnston et al. 2001[26]	Baseline height (cm)	113.2 (93.2 to 135.1) GEN 114.9 (93.6 to 139.2) GEN + ES	114.0 (94.6 to 140.0)	NR
	Height (cm) after 5.6 years of treatment	146.2 ± 5.3 (GEN) 148.2 ± 4.6 (GEN + ES)	ES first year then ES + GEN after = 145.5 ± 4.6	NS

CGHAC = Canadian Growth Hormone Advisory Committee; ES = estrogen; GEN = Genotropin; Height SDS = height standard deviation score; HUM = Humatrope; NR = not reported; NS = not significant; SD = standard deviation; Soma = somatropin.

Height Standard Deviation Score

Statistically significant differences between groups were reported for Height SDS in Stephure and CGHAC[6] and Davenport et al.[27] with higher scores reported in the somatropin-treated groups than in the untreated groups. Change in Height SDS was reported to be statistically higher in the somatropin-treated group than in the untreated group by Stephure and CGHAC,[6] while Johnston et al.[26] reported statistically higher change in Height SDS in the first year of treatment in the treated group versus the untreated group; however, after the untreated group received Genotropin, this difference was no longer statistically significant. Finally, changes in Height SDS reported by Kollmann et al.[30] favoured patients receiving somatropin 2 IU/m^2/day or 3 IU/m^2/day compared with the untreated patients; however, the statistical significance of between-treatment comparisons was not reported (Table 6). In the Li et al. review,[5] the mean difference for the change in Height SDS reported in the Johnston et al.[26] and Kollmann et al.[30] studies were pooled to yield a WMD in Height SDS of 0.73 (95% confidence interval [CI], 0.33 to 1.13), indicating greater growth with somatropin treatment compared with no treatment.

TABLE 6: SUMMARY OF HEIGHT SDS AND CHANGE IN HEIGHT SDS FROM BASELINE IN THE TAKEDA AND LI REVIEWS

Study	Outcomes (mean ± SD)	Somatropin	Control	*P* Value
Stephure et al. 1993[43]; Stephure and CGHAC 2005[6] (5.7 ± 1.6 years since randomization)	Height SDS (age-specific Turner)[a]	1.4 ± 1.0	0.2 ± 0.9	< 0.001
	Height SDS (adult Turner)[b]	0.7 ± 0.9	–0.3 ± 0.8	< 0.001
	Change in Height SDS (age-specific Turner)	1.6 ± 0.6	0.3 ± 0.4	< 0.001
Stephure and CGHAC 2005[6] (10.6 ± 1.7 years since randomization)	Height SDS (age-specific Turner)[a]	0.9 ± 0.9	–0.1 ± 1.0	< 0.001
	Height SDS (adult Turner)[b]	0.9 ± 0.9	–0.1 ± 1.0	< 0.001
	Change in Height SDS (age-specific Turner)[b]	1.1 ± 0.5	0.0 ± 0.5	< 0.001
Davenport et al. 2007[27]	Height SDS	–0.34 ± 1.10	–2.16 ± 1.22	< 0.0001
Johnston et al. 2001[26]	Change in Height SDS in first year	0.7 ± 0.7 (GEN) 1.0 ± 0.9 (GEN+ES)	0.4 ± 0.9	< 0.05
	Change in Height SDS at the end of year 5	1.6 ± 0.9 (GEN) 1.8 ± 0.9 (GEN+ES)	1.2 ± 0.7	NS
Kollmann et al. 1991[30]	Change in Height SDS in first year	0.62 ± 0.92 (Soma 2 IU/m^2/day) 0.82 ± 1.07 (Soma 3 IU/m^2/day)	–0.01 ± 0.95	NR

CGHAC = Canadian Growth Hormone Advisory Committee; ES = estrogen; GEN = Genotropin; Height SDS = height standard deviation score; IU = international unit; NR = not reported; NS = not significant; SD = standard deviation; Soma = somatropin.
[a]Height relative to the distribution of height in children of the same chronological age.
[b]Height relative to the distribution of height in adults with TS.

Height Velocity

Height velocity was statistically significantly greater in somatropin-treated patients compared with those receiving placebo or no treatment (Table 7). In two RCTs,[27,43] HV slowed in the second year compared with that in the first year in both treatment groups.

TABLE 7: SUMMARY OF HEIGHT VELOCITY IN THE TAKEDA AND LI REVIEWS

Study	Outcomes, cm/year (mean ± SD)	Somatropin	Control	*P* Value
Stephure et al. 1993[43]; Stephure and CGHAC 2005[6]	HV at 1st year HV at 2nd year	7.60 ± 1.2 6.00 ± 1.1	4.20 ± 1.1 3.80 ± 1.2	NR
Quigley et al. 2002[3]	HV 0 to 18 months	For 0.27 mg/kg/week: 6.6 ± 1.1 For 0.36 mg/kg/week: 6.8 ± 1.1	4.2 ± 1.1	< 0.001
Davenport et al. 2007[27]	HV after 1st year	11.7 ± 2.4	8.0 ± 2.4	< 0.0001
	HV after 2nd year	8.4 ± 1.6	5.5 ± 1.8	< 0.0001
Rosenfeld 1990[31]	HV in groups with OX HV in groups without OX	9.80 ± 1.40 6.60 ± 1.20	 3.80 ± 1.10	< 0.05

CGHAC = Canadian Growth Hormone Advisory Committee; HV = height velocity; NR = not reported; OX = oxandrolone; SD = standard deviation.

Height Velocity Standard Deviation Score

RCTs in both systematic review reported HVSDS. HVSDS were more favourable in somatropin-treated groups than in the untreated groups; however, the statistical significance of these differences was not always reported (Table 8).

TABLE 8: SUMMARY OF HEIGHT VELOCITY STANDARD DEVIATION SCORE IN THE TAKEDA AND LI REVIEWS

Study	Outcomes (mean ± SD)	Somatropin	Control	*P* Value
Stephure et al. 1993[43]; Stephure and CGHAC 2005[6]	HVSDS at 1st year HVSDS at 2nd year	3.40 ± 1.60 2.30 ± 1.10	0.20 ± 1.00 0.70 ± 1.30	NR
Davenport et al. 2007[27]	HVSDS after 1st year	1.75 ± 1.25	–0.83 ± 0.95	< 0.0001
	HVSDS after 2nd year	0.70 ± 1.11	–1.63 ± 1.29	< 0.001
Rosenfeld 1990[31]	HVSDS in groups with OX HVSDS in groups without OX	6.60 ± 1.20 3.10 ± 1.20)	 –0.10 ± 1.00	NR

CGHAC = Canadian Growth Hormone Advisory Committee; HVSDS = height velocity standard deviation score; NR = not reported; OX = oxandrolone; SD = standard deviation.

Results from the comparative observational studies.

Data pooling for final height and Height SDS was performed in the four prospective observational studies included in the Li et al. review.[5] A significantly higher final height in somatropin-treated patients when compared with patients not receiving somatropin was observed: WMD (95% CI) of final height was 5.86 cm (95% CI, 4.30 to 7.41), favouring somatropin treatment. Two prospective studies reported significantly higher Height SDS in the somatropin-treated patients than patients not receiving somatropin: WMD 1.08 (95% CI, 0.78 to 1.38), favouring somatropin treatment. Heterogeneity was high in the retrospective studies, so results were not pooled. Results are shown in Table 9.

TABLE 9: SUMMARY OF FINAL HEIGHT AND HEIGHT STANDARD DEVIATION SCORE — OBSERVATIONAL STUDIES

Study	Somatropin		Control		Weight %	WMD (95% CI) [a]
	N	(mean ± SD)	N	(mean ± SD)		
Final Height						
Prospective studies						
Pasquino et al. 1990[40]	18	147.60 ± 7.30; N = 18	18	142.20 ± 4.90	14.64	5.40 [1.34 to 9.46]
Hochberg and Zadik[38]	25	147.30 ±4.90	24	142.90 ± 5.10	30.76	4.40 [1.60 to 7.20]
Pasquino et al. 2005[41]	60	151.10 ± 6.10	59	144.30 ± 5.60	54.60	6.80 [4.70 to 8.90]
Total (95% CI)	103		101		100.00	5.86 [4.30 to 7.41]
Retrospective studies						
Dacou-Voutetakis et al. 1998[37]	35	146.10 ± 6.60	27	144.00 ± 6.10	27.35	2.10 [–1.07 to 5.27]
Bertelloni et al. 2000[36]	14	148.10 ± 3.00	12	142.00 ± 2.80	55.35	6.10 [3.87 to 8.33]
Bechtold et al. 2006[35]	65	150.59 ± 5.80	12	147.30 ± 6.60	17.30	3.29 [–0.70 to 7.28]
Total (95% CI)	114		51		100.00	NR
Height SDS						
Prospective studies						
Pasquino et al.[40]	18	0.90 ± 1.20	18	0.04 ± 0.80	20.47	0.86 [0.19 to 1.53]
Pasquino et al.[41]	60	1.50 ± 0.98	59	0.36 ± 0.90	79.53	1.14 [0.80 to 1.48]
Total (95% CI)	78		77		100.00	1.08 [0.78 to 1.38]
Retrospective studies						
Dacou-Voutetakis et al.[37]	35	0.24 ± 1.00	27	0.07 ± 0.90	39.78	0.17 [–0.30 to 0.64]
Bertelloni et al.[36]	14	–2.40 ± 0.50	12	–3.40 ± 0.50	60.22	1.00 [0.61 to 1.39]
Total (95% CI)	49		39		100.00	NR

CI = confidence interval; Height SDS = height standard deviation score; N = number of patients; NR = not reported; SD = standard deviation; WMD = weighted mean difference.
Source: Li et al. 2007.[5]
[a]Data were pooled using fixed effect model.

d) Summary of quality of life reported in the systematic reviews

Takeda et al.[4] reported that none of the included studies reported quality of life (QoL) data.

Li et al.[5] reported results of QoL from two RCTs[33,44] and found that QoL data are sparse and it is difficult to make definitive conclusions as to whether QoL is improved in patients treated with somatropin when compared with those not treated with somatropin. Rovet and Holland[44] found that patients who were receiving somatropin seemed to do better than those not treated with somatropin in most evaluated psychological aspects; however, a decrease in mathematics performance with time in the treated group compared with the control group was indicated by parental ratings of school performance. Ross et al.[33] reported no difference in general cognitive function between somatropin-treated and control groups. Verbal and non-verbal abilities were similar in both treated and untreated groups, except in one measure of memory (delayed recall of the Rey Complex), in which the somatropin-treated group performed better.

e) Summary of biochemical markers reported in the systematic reviews

Biochemical markers were not an outcome of interest in the Li et al. systematic review.[5]

Takeda et al.[4] reported biochemical outcomes from three RCTs;[27-29] Table 10 presents the biochemical outcomes of interest based on the CDR review protocol. Mean levels of IGF-1 at end of treatment were reported in two studies.[28,29] In both studies, statistically significantly higher IGF-1 levels were reported in somatropin-treated groups compared with the untreated groups. Compared with the untreated group after two years of treatment, significantly higher IGF-1 standard deviation scores (SDSs) were reported by Davenport et al. 2007 in the somatropin-treated group. Two studies provided data regarding fasting blood glucose, and both reported higher fasting blood glucose in the somatropin-treated groups than in the untreated groups.

TABLE 10: BIOCHEMICAL MARKERS REPORTED IN THE TAKEDA AND LI SYSTEMATIC REVIEWS

Study	Outcome	Somatropin	Control	*P* Value
Davenport et al. 2007[27]	IGF-1 SDS	1.26 ± 0.72	–0.69 ± 0.84	< 0.0001
	ΔIGF-1 SDS[a]	1.53 ± 0.93	–0.09 ± 0.87	NR
Gravholt et al. 2002[28]	IGF-1 (mcg/L)	380.5 ± 116.3	179.8 ± 79.4	< 0.0005
	fasting blood glucose (mmol/L)	4.28 ± 0.59	4.02 ± 0.44	0.046
Gravholt et al. 2005[29]	IGF-1 (mcg/L)	661 ± 192	288 ± 69	NR
	fasting blood glucose (mmol/L)	4.46 ± 0.40	4.04 ± 0.47	Unclear

IGF-1 = insulin-like growth factor-1; mcg = microgram; mmol = millimole; NR = not reported; SDS = standard deviation score.
[a]Change in IGF-1 SDS from baseline.

f) Summary of adverse events of the included studies in the systematic reviews

Safety data were inadequately reported in the two systematic reviews, partly because the safety data were insufficiently presented in the included individual trials. All RCTs that had safety data, except the Rosenfeld study[31] (few adverse events were experienced in patients receiving somatropin), reported a numerically higher incidence of treatment-related adverse events in the somatropin groups compared with no treatment or placebo. The most frequently reported adverse events in somatropin-treated patients included surgical procedures, otitis media, ear disorder, joint disorder, respiratory disorder, and sinusitis.

In the Stephure study,[6] patients treated with somatropin were more likely to experience serious adverse events (SAEs) than untreated patients, while the Davenport et al.[27] study reported no difference in SAEs between somatropin and untreated patients.

Li et al.[5] summarized adverse events reported in five[34,38-40,42] comparative observational studies. A slightly higher prevalence and incidence of fracture between patients who received somatropin versus those who didn't receive it were reported by Bakalov et al.[34]; results are presented in Table 11. No quantitative data were reported by Naeraa et al.,[39] Pasquino et al.,[40] and Taback et al.[42]; however, they noted that during growth hormone treatment, there were no serious side effects observed, and Hochberg and Zadik[38] mentioned that there were no apparent adverse events and that somatropin therapy was well tolerated.

TABLE 11: SUMMARY OF ADVERSE EVENTS REPORTED IN THE TAKEDA AND LI SYSTEMATIC REVIEWS; n (%)

Study	AEs	Somatropin	Control
Stephure and CGHAC 2005[6] Humatrope 0.30 mg/kg/ week (n = 74) versus no treatment (n = 64)[a]	Surgical procedures	37 (50.0)	17 (26.6)
	Otitis media	35 (47.3)	17 (26.6)
	Ear disorder	15 (20.3)	4 (6.3)
	Joint disorder	10 (13.5)	2 (3.1)
	Respiratory disorder	8 (10.8)	1 (1.6)
	Sinusitis	14 (18.9)	4 (6.3)
	Goitre	0 (0)	4 (6.3)
	Death (ruptured aortic aneurysm)	0 (0)	1 (1.6)
	Elevated transamine levels	1 (1.4)	0 (0)
	Intracranial hypertension	1 (1.4)	0 (0)
	SAEs	27%	13%
Davenport et al. 2007[27] Humatrope (n = 41) versus no treatment (n = 37); 2 years	Serious AEs	4 (9)	4 (9)
	Treatment-emergent AEs	42 (93)	43 (98)
Quigley et al. 2002[3] Humatrope 0.27 mg/kg/week (n = 45) versus placebo (n = 41)	Otitis media (occurrence/worsening)	54 (29)	6 (13)
Bakalov et al. 2004[34] Observational study Soma (n = 23) versus no Soma (n = 23)	Fracture prevalence	7 (30)	5 (22)
	fracture incidence (per 100 TS patient years)	2.2 (per 100 patient-years)	1.0 (per 100 patient-years)

AE = adverse event; CGHAC = Canadian Growth Hormone Advisory Committee; n = subpopulation; NR = not reported; SAE = serious adverse event; Soma = somatropin; TS = Turner syndrome.
[a]SAE for the Canadian RCT mainly reported by Stephure and CGHAC were reported in Quigley et al. 2005.[47]

g) Summary of Takeda et al. and Li et al. systematic reviews

Both the Takeda et al.[4] and Li et al.[5] systematic reviews used acceptable methods to identify, extract, appraise, and summarize studies; however, restriction to English language publications and not assessing publication bias are some limitations. Inclusion in the Takeda et al. systematic review[4] was restricted to RCTs, which would be expected to provide the most high-quality evidence. However, inclusion of observational studies in the Li et al. review[5] would be expected to increase the generalizability of findings. Results from RCTs and comparative observational studies were consistent in reporting greater and more rapid gains in height and height velocity in patients treated with somatropin, compared with no treatment. In addition, when reported it was found that IGF-1 levels and levels of fasting glucose were higher in the somatropin-treated group. Both reviews indicated that adverse event data were sparsely reported. The Takeda et al. review[4] did not identify any QoL data within the included studies, whereas the Li et al. review[5] identified two studies reporting QoL data; however, these data were sparsely reported.

3.3.2 Summary of the Properties of Somatropin Products Available in Canada

Given the large number of somatropin products already available in Canada, we describe the similarities and differences between the available products.

The following somatropin products are presented in this section: Genotropin, Omnitrope, Humatrope, Nutropin, Saizen, and Norditropin. Serostim, another somatropin product available in Canada, has been omitted from this comparison because it is exclusively indicated for the treatment of HIV wasting associated with catabolism, weight loss, or cachexia. The information presented in Table 12, Table 13, Table 14, and Table 15 was obtained from the current Canadian product monographs.[13-18,44,48] It is important to note that the respective monographs have slight differences in the content, layout, and types of information. This is likely due to the time of approval, which could explain the differences in product monograph requirements.

a) Manufacturing Information, Formulations, Indications, Dosing

As illustrated in Table 12, all products use recombinant DNA technology in *Escherichia coli* host cells except for Saizen, which is produced in mammalian source host cells. Biological activity was not reported for all products, but when reported it is 3 IU = 1 mg. Although not always reported, it is likely that all products contain some host cell impurities in the final formulation. The excipients used as preservatives or stabilizers vary greatly between formulations (lyophilized powder and solution) as well as between products. Some of the products contain benzyl alcohol, which is contraindicated in newborns. While all products except Norditropin are indicated for the treatment of GHD in children and adults, several of the products have additional indications for the treatment of TS (Genotropin, Humatrope, Nutropin, and Saizen), idiopathic short stature, small for gestational age, chronic renal insufficiency, or failure and short-stature homeobox-containing gene (SHOX).

All products, excepting Omnitrope and Norditropin, offer a lyophilized powder formulation that requires reconstitution prior to administration (Table 13). In addition, several products offer a stabilized solution either in a vial or in a pen with a cartridge ready for injection. All products are recommended for subcutaneous injection, and Nutropin, Humatrope, and Saizen can also be administered by intramuscular injection. The proprietary products are variable in their concentrations and administration formats. This is consistent with the variability in the recommended dosing for the different products, although the dosing recommendations for pediatric GHD and TS appear to be more consistent between products than those for adult GHD. The inconsistency in formulations and in dosing recommendations adds to the complexity when a patient is switched from one product to another and could increase the potential for dosing errors.

b) Pharmacokinetics and Pharmacodynamics

Although there are slight differences in the pharmacokinetic profiles of the different somatropin products based on the available information (Table 14), these differences do not appear to be significant and are not expected to result in important clinical consequences. There is limited information on the pharmacodynamic properties of a number of somatropin products in Canada. Genotropin appears to be very similar in its pharmacodynamic properties to Omnitrope (see Table 15).

TABLE 12: DESCRIPTION OF SOMATROPIN PRODUCTS

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
Genotropin	Recombinant DNA technology. Uses *E. coli* that is modified by addition of the human growth hormone gene	Not mentioned	Preparations of Genotropin contain a very small amount of PECP.	5.8 mg, 5.3 mg, and 12 mg/pen cartridge: glycine, mannitol, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, m-Cresol, and water for injection	Pediatric GHD, SGA, TS, ISS, and Adult GHD
				0.2 mg to 2.0 mg/syringe: glycine, mannitol, sodium dihydrogen phosphate anhydrous, disodium phosphate anhydrous, and water for injection	
Omnitrope	Recombinant DNA technology. Uses *E. coli* that is modified by addition of the human growth hormone gene	3.0 IU/ 1 mg	Contains small amount of host cell *E. coli* peptide (HCP).	5.8 mg/vial: glycine, disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dehydrate, and diluent supplied bacteriostatic water containing 1.5% benzyl alcohol	Pediatric and Adult GHD
				5 mg/1.5 mL pen cartridge: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, poloxamer 188, mannitol, benzyl alcohol, and water for injection	
				10 mg/1.5 mL pen cartridge: disodium hydrogen phosphate heptahydrate, sodium dihydrogen phosphate dihydrate, poloxamer 188, phenol, glycine, and water for injection	

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
Humatrope	Recombinant DNA technology. Uses *E. coli* that is modified by addition of the human growth hormone gene	Not mentioned	Not mentioned	5.0 mg/vial: mannitol, glycine, dibasic sodium phosphate, phosphoric acid and/or sodium hydroxide may have been used for pH adjustment; water for injection with glycerin and metacresol	Pediatric GHD, SHOX, TS, ISS, SGA and Adult GHD
				6 mg, 12 mg, and 24 mg/cartridge: mannitol, glycine, dibasic sodium phosphate, phosphoric acid and/or sodium hydroxide may have been added to adjust the pH; water for injection, metacresol glycerin.	
Nutropin	Recombinant DNA technology. Uses *E. coli* that is modified by addition of the human growth hormone gene	Not mentioned	Not mentioned	10.0 mg/vial: glycine, mannitol, sodium phosphate dibasic, sodium phosphate monobasic, and benzyl alcohol	Pediatric GHD, growth failure due to renal insufficiency, TS, and Adult GHD
				10 mg/2 mL vial: phenol, polysorbate 20, sodium chloride, sodium citrate	
				10 mg/2 mL pen cartridge: phenol, polysorbate 20, sodium chloride, sodium citrate	
				5 mg/2 mL, 10 mg/2 mL and 20 mg/2 mL NuSpin cartridge: phenol, polysorbate 20, sodium chloride, sodium citrate	
Saizen	Recombinant DNA technology. Uses mammalian cell expression system (C127 mouse cells)	3.0 IU/1 mg	Not mentioned	3.3 mg/vial: mannitol, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate	Pediatric GHD, SGA, TS, chronic renal failure and Adult GHD
				5 mg/vial: phosphoric acid, sodium hydroxide, sucrose	

Drug	Manufacturing Process	Biological Activity	Impurities	Excipients	Indications
				8.8 mg (5.83 mg/mL) click.easy: phosphoric acid, sodium hydroxide, sucrose and cartridge of bacteriostatic solvent	
				6 mg (5.83 mg/mL), 12 mg (8 mg/mL) and 20 mg (8 mg/mL) cartridges: citric acid, phenol, poloxamer 188, and sucrose	
Norditropin	Recombinant DNA technology. Uses *E. coli* that is modified by addition of the human growth hormone gene	Not mentioned	Not mentioned	5 mg/1.5 mL, 10 mg/ 1.5 mL and 15 mg/ 1.5 mL cartridges or pens: histidine, poloxamer 188, phenol, mannitol, HCl/NaOH, and water for injection	Pediatric GHD and SGA

E. coli = *Escherichia coli*; GHD = growth hormone deficiency; HCl = hydrogen chloride; HCP = host cell proteins; ISS = idiopathic short stature; IU = international unit; lyo = lyophilized; mL = millilitres; mg = milligrams; NaOH = sodium hydroxide; PECP = periplasmic *Escherichia coli* peptides; SGA = small for gestational age; SHOX = short-stature homeobox-containing gene; TS = Turner syndrome.

TABLE 13: PHYSICAL DESCRIPTION AND DOSING OF SOMATROPIN PRODUCTS

Drug	Formulation	Strength	Administration	Dosing		
				Pediatric GHD	Adult GHD	Turner syndrome
Genotropin	Lyo powder in a 2 chamber pen cartridge	5 mg, 5.3 mg, and 12 mg/pen	Reconstitution and then sc injection	0.16 to 0.24 mg/kg/week divided into 6 to 7 sc injections/week	0.15 to 0.3 mg/day to a max of 1.33 mg/day	0.33 mg/kg/week divided into 6 to 7 sc injections
	Lyo powder in a 2-chamber glass cartridge	0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg/ syringe				
Omnitrope	Lyo powder[a]	5.8 mg/vial	Reconstitution and then sc injection	0.025 to 0.035 mg/kg/day	0.15 to 0.3 mg/day to a max of 1.33 mg/day	No indication
	Solution in pen cartridges	5 mg/1.5 mL, 10 mg/ 1.5 mL	sc injection			
Humatrope	Lyo powder	5.0 mg/vial	Reconstitution and then sc or im injection	0.18 mg/kg/week given on 3 alternate days or 6 to 7 injections/week to a maximum of 0.3 mg/kg/week	Start dose of 0.006 mg/kg/day max dose 0.0125 mg/kg/day	0.375 mg/kg/week given on 3 alternate days or daily
	Lyo powder cartridge and diluent syringe	6 mg, 12 mg, and 24 mg/cartridge				
Nutropin	Lyo powder	10.0 mg/vial	Reconstitution and then im or sc injection	Up to 0.3 mg/kg/week divided into 7 injections/week	Start dose of 0.042 mg/kg/week Max dose 0.175 mg/kg/week in patients younger than 35 years and max dose 0.0875 mg/kg/week in patients older than 35 years divided into 7 injections /week	Up to 0.375 mg/kg/week divided into equal doses, 3 to 7 injections/week by sc injection
	Solution	10 mg/2 mL vial	Im or sc injection			
	Solution in pen cartridge	10 mg/2 mL pen cartridge	Sc injection			
	Solution in NuSpin injection device	5 mg/2 mL, 10 mg/2 mL, or 20 mg/2 mL cartridges	Sc injection			

Drug	Formulation	Strength	Administration	Dosing		
				Pediatric GHD	Pediatric GHD	Pediatric GHD
Saizen	Lyo powder	3.33 mg/vial and 5 mg/vial	Reconstitution & then im or sc injection	0.2 to 0.27 mg/kg/week	Start dose of 0.005 mg/kg/day dose may be increased to 0.01 mg/kg/day after 4 weeks	0.375 mg/kg/week
	Lyo powder in a click.easy	8.8 mg (5.83 mg/mL)/ click.easy	Reconstitution & then sc injection			
	Solution for injection in a cartridge	6 mg (5.83 mg/mL), 12 mg (8 mg/mL), and 20 mg (8 mg/mL)/ cartridge	Sc injection			
Norditropin	Solution for injection in a cartridge	5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL / cartridge	Sc injection	daily up to 0.043 mg/kg/day		
	Solution for injection in pen	5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL / pen	Sc injection			

GHD = growth hormone deficiency; im = intramuscular; kg = kilogram; lyo = lyophilized; max = maximum; mg = milligram; sc = subcutaneous.
[a]Lyophilized powder not marketed in Canada.

TABLE 14: PHARMACOKINETIC PROFILE OF SOMATROPIN PRODUCTS

Pharmacokinetics	AUC (h*mcg/L)	Cmax (mcg/L)	Tmax (h)	$T_{1/2}$ (h)	Bioavailability (%)	Elimination (L/h/kg)	Metabolism
Genotropin[a] 5 mg of 5.8 mg/vial Lyo powder	592 ± 131[a]	78 ± 27[a]	4 (2.0 to 8.0)[a]	2.6 ± 0.7[a]	Approx. 80%	NR	Liver and kidneys
Omnitrope[a] 5 mg of 5.8 mg/vial Lyo powder	566 ± 147	71 ± 24	4.0 (2.0 to 6.0)	3.2 ± 0.7	Approx. 80%	Clearance 0.14 (± 0.04)	Liver and kidneys
5 mg of 5 mg/1.5 mL solution	546 ± 140	72 ± 28	4.0 (2.0 to 8.0)	2.8 ± 0.7			
Humatrope	NR	NR	NR	3.8 for sc and 4.9 for im	Approx. 75% after sc and 63% after im	Clearance 0.14	Liver and kidneys
Nutropin 0.1 mg of Lyo powder	626	56.1	7.5	7.5	NR	Clearance 0.116 to 0.174	Liver and kidneys
0.1 mg of solution	673	71.1	3.9	2.3		Clearance 0.116 to 0.174	
0.05 mg of solution	486	72.5	4.2	2.22		Clearance 0.106	
Saizen Lyo powder 8.8 mg	320 (205 to 495)	45.1 (21.5 to 69.2)	4 (2.0 to 7.0)	2.7 (1.2 to 5.8)	70% to 90%	Clearance 15 L/h	NR
Norditropin 2.5 mg/m^2 (0.085 mg/kg)	397 to 408	42 to 46	4	2.6	NR	0.072 to 0.234	Liver and kidneys
5 mg (0.054 to 0.082 mg/kg)	396 to 433	39 to 43	4 to 4.5	3			

AUC = area under the concentration curve; Cmax = maximum plasma concentration of drug; h = hour; im = intramuscular; kg = kilogram; L = litre; lyo = lyophilized; mcg = microgram; mg = milligram; mL = millilitre; NR = not reported; sc = subcutaneous; Tmax = time to reach maximum concentration of the drug; $T_{1/2}$ = drug half-life.
[a]Data from comparative pharmacokinetic and pharmacodynamic trial of Omnitrope versus Genotropin (EP00-104).

TABLE 15: PHARMACODYNAMIC PROFILE OF SOMATROPIN PRODUCTS

Pharmacodynamics IGF-1	AUEC (h-mcg/L)	Emax (mcg/L)	$Tmax_E$ (h)
Genotropin[a] (5 mg of 5.8 mg/vial Lyo powder[a]	15,960 ± 3,557	209 ± 49	24 (12 to 48)
Omnitrope[a] 5 mg of 5.8 mg/vial Lyo powder	16,712 ± 3,847	218 ± 56	24 (12 to 48)
5 mg of 5 mg/1.5 mL solution	16,295 ± 3,664	213 ± 49	24 (12 to 48)
Humatrope	NR	NR	NR
Nutropin	NR	NR	NR
Saizen	NR	NR	NR
Norditropin 0.0009 to 0.009 mg/kg	NR	241	NR

AUEC = area under the effective concentration curve; Emax = maximum effect of drug; h = hour; IGF-1 = insulin-like growth factor-1; kg = kilogram; L = litre; lyo = lyophilized; mcg = microgram; mg = milligram; mL = millilitre; NR = not reported; $Tmax_E$ = time to reach maximum effect of the drug.
[a]Data from comparative pharmacokinetic and pharmacodynamic trial of Omnitrope versus Genotropin (EP00-104).

4. DISCUSSION

4.1 Summary of Available Evidence

No RCTs met the protocol for inclusion in the systematic review comparing Genotropin with other somatropin products for the treatment of short stature associated with TS, and no indirect comparisons of the different somatropin products available in Canada were identified by CDR. Thus, CDR — in consultation with the clinical expert contracted for the review — identified two key clinical issues to consider in the review of Genotropin: a summary of systematic reviews of the efficacy and /or safety of somatropin TS, and a comparison of the properties of the somatropin products available in Canada.

4.2 Interpretation of Findings

Of the somatropin products approved by Health Canada, only Humatrope, Nutropin, Saizen, and now Genotropin have a Health Canada indication for treatment of short stature associated with TS. The four products are variable in their concentration and administration formats, with the recommended dose being lower for Genotropin (0.33 mg/kg/week) than for the other three products (0.375 mg/kg/week). In addition, there are differences in the pharmacokinetic profiles of the different products; however, these differences are slight and are not expected to result in important clinical differences. The clinical expert consulted for this review indicated that clinicians consider all somatropin products to be similarly efficacious and safe, with their primary distinguishing features being their formulation (powder versus solution), injection device (syringes versus pens), potential to cause stinging at the injection site, and cost. The clinical expert noted that product selection is generally based upon patient and/or parent preference in consultation with the clinician, and that switching between products is not a frequent occurrence. However, it is noted that because of the difference in the recommended dose between Genotropin and other somatropin products indicated for TS, there is the potential for dosing errors when switching between products.

While studies directly comparing somatropin products are lacking, two systematic reviews (Takeda et al.[4] and Li et al.[5]) provide evidence of the benefits and harms of somatropin generally in girls with TS. There appeared to be some disagreement between the authors of the systematic reviews regarding the quality of the included RCTs, despite the overlap in the trials included. This is likely related to the instruments used by the authors of the systematic reviews to assess the quality of included studies. However, despite concerns over the quality of some studies, the study results were consistent in reporting more rapid and greater gains in height with somatropin compared with no treatment. One of two RCTs identified in the Li et al. review[5] as being of good quality (Stephure and CGHAC[6]) was a Canadian study that also had the longest duration of treatment and follow-up of all RCTs. Results from Stephure and CGHAC indicate that somatropin treatment produces an average long-term gain in height of approximately 9 cm, compared with no treatment. Results from prospective observational studies were consistent with those of RCTs in reporting a statistically higher final height and height SDS for somatropin-treated persons compared with those not receiving somatropin. The clinical significance of the magnitude of height gain achieved with somatropin is a matter of debate,[49] and there is debate as to whether short stature is a disability or not.[5] No minimal clinically important difference for height change was identified by CDR.

Only one of the systematic reviews (Li et al.[5]) provided data related to HRQoL, noting that HRQoL data were sparse, variable, and inconclusive. One of the disadvantages of the HRQoL measures used in the included studies is that the instruments were not developed specifically for patients with TS. Li et al.[5] concluded that the evidence supporting the idea that an increase in height would improve a patient's HRQoL is equivocal.

Takeda et al.[4] and Li et al.[5] reported that AE data were sparsely reported. Higher rates of AEs were reported by the Canadian RCT[6] in patients receiving somatropin compared with those not receiving somatropin, with the most frequently reported AEs, reported in > 20% of patients in either the somatropin or control group, being surgical procedures (50% versus 27%), otitis media (47% versus 27%), and ear disorders (20.3% versus 6.3%), respectively. These findings are reflected in the Genotropin product monograph, which states that patients with TS have an increased risk of ear and hearing disorders; hence, these patients should be evaluated carefully for otitis media and other ear disorders before and during treatment with somatropin.[13] In addition, significantly higher IGF-1 concentrations were reported in patients receiving somatropin versus no treatment; the Genotropin product monograph indicates that IGF 1 concentrations should be monitored regularly and maintained within the normal range for age and sex.[13]

5. CONCLUSIONS

Based on the findings of two systematic reviews, it appears that somatropin treatment results in greater and more rapid gains in height, including final height, compared with no treatment. However, whether QoL is improved in those treated with somatropin compared with those not treated is uncertain. Genotropin is one of several somatropin products approved by Health Canada for the treatment of short stature associated with TS; others include Humatrope, Nutropin, and Saizen. There is insufficient evidence on the comparative efficacy and safety of the somatropin products for the treatment of short stature associated with TS. In clinical practice, product selection is generally based upon patient and/or parent preference in consultation with the clinician.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed.

No patient input was received regarding the use of Genotropin for Turner syndrome.

APPENDIX 2: EXCLUDED STUDIES

Reference	Reason for Exclusion
Final report of study TRN 87-055: treatment with Genotropin in girls with Turner syndrome. A multi-centre clinical trial in Belgium (CONFIDENTIAL internal manufacturer's report). Stockholm: Kabi Pharmacia; 1993 Jan 28.	Wrong comparator
Ferrandez A, et al. Acta Paediatrica Scandinavica, Supplement. 1989; 78(356):87-91.	
Job JC, et al. Horm Res. 1991;35(6):229-33.	
Johnston DI, et al. Arch Dis Child. 2001;84(1):76-81.	
Massa G, et al. Clin Endocrinol (Oxf). 1993;38(3):253-60.	
Menke LA, et al. J Clin Endocrinol Metab. 2010;95(3):1151-60.	
Menke LA, et al. Clin Endocrinol (Oxf). 2010;73(2):212-9.	
Takano K, et al. Horm Res. 1993;39(Suppl 2):37-41.	
Vanderschueren-Lodeweyckx M, et al. J Clin Endocrinol Metab. 1990;70(1):122-6.	
Wisniewski A. Pediatria Polska. 2003;78(7):607-17.	
Ranke MB, et al. Horm Res Paediatr. 2011;76 Suppl 3:48-50.	Not randomized controlled trial
Ranke MB, et al. Horm Res Paediatr. 2011;75(6):423-32.	
Ranke MB, et al. Horm Res Paediatr. 2012;78(1):8-17.	
Bryant J, et al. Health Technol Assess. 2002;6(18):1-168.	Systematic review
Cave CB, et al. Cochrane Database Syst Rev. 2003;(3).	
Loftus J, et al. J Pediatr Endocrinol. 2010 Jun;23(6):535-51.	
Takeda A, et al. Health Technol Assess. 2010;14(42):1-237.	

APPENDIX 3: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to 2013 July 19 Ovid MEDLINE In-Process & Other Non-Indexed Citations Ovid MEDLINE Daily and Ovid MEDLINE 1946 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 22, 2013
Alerts:	Weekly search updates began July 22, 2013 and ran until November 20, 2013.
Study Types:	No filters used.
Limits:	No date or language limits used. Conference abstracts excluded.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	Subject headings
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.af	All fields
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
.tn	Drug trade name
.mf	Drug manufacturer

MULTI-DATABASE STRATEGY	
Line #	**Strategy**
1	(Genotrop* or Genotonorm*).af.
2	(CB-311 or LY-137998 or SJ-0011 or SR-29001 or CB311 or LY137998 or SJ0011 or SR29001).ti,ot,ab,sh,rn,hw,nm.
3	exp human growth hormone/ or exp growth hormone derivative/ or exp recombinant growth hormone/
4	(growth hormone* or HGH or r-HGH or rhgh).ti,ab.
5	somatrop*.ti,ab.
6	exp somatropin/
7	(NQX9KB6PCL or 12629-01-5).rn,nm.
8	or/3-7
9	(Pfizer* or Pharmacia or Upjohn or Kabi).ti,ab,ot,hw,rn,nm,tn,mf.
10	8 and 9
11	(KIGS or KIMS).ti,ab.
12	1 or 2 or 10 or 11
13	Turner syndrome/
14	(Turner* adj2 syndrome*).ti,ab.
15	((Ullrich adj1 Turner*) or (Bonnevie adj1 Ullrich*)).ti,ab.
16	((Morgagni adj2 Turner adj2 Albight) or (Turner adj1 Varny) or (Schereshevki* adj1 Turner) or (Turner* adj1 phenotype*)).ti,ab.
17	("45,X" or "45,XO" or "45,X0" or monosomy-X).ti,ab.
18	(X-chromosome adj1 (monosomy or mosaicism)).ti,ab.
19	((XO adj1 (syndrome or karyotype)) or pterygolymphangiectasia).ti,ab.
20	Gonadal Dysgenesis/ or Gonadal Dysgenesis, Mixed/
21	(gonadal adj1 (dysgenesis or agenesis)).ti,ab.
22	or/13-21
23	12 and 22
24	remove duplicates from 23
25	24 not conference abstract.pt.

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and other)	Same keywords, limits used as per MEDLINE search

Grey Literature

Dates for Search:	July 2013
Keywords:	Included terms for Genotropin and Turner syndrome
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug Regulatory Approvals
- Advisories and Warnings
- Databases (free)
- Internet Search.

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4. Takeda A, Cooper K, Bird A, Baxter L, Frampton GK, Gospodarevskaya E, et al. Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation. Health Technol Assess [Internet]. 2010 [cited 2013 Aug 9];14(42):1-237. Available from: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0011/65279/FullReport-hta14420.pdf
5. Li H, Banerjee S, Dunfield L, Kirby J, Jones M, Hamilton J, et al. Recombinant human growth hormone for treatment of Turner syndrome: systematic review and economic evaluation [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007. [cited 2013 Aug 21]. (Technology report number 96). Available from: http://www.cadth.ca/media/pdf/461_Turner-Syndrome_tr_e.pdf
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13. Genotropin GoQuick and Genotropin MiniQuick: somatropin (rDNA origin) for injection [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2013 Feb.
14. Humatrope (somatropin for injection). Biosynthetic human growth hormone of recombinant DNA origin: 5 mg vial; 6, 12, 24 mg cartridges [product monograph]. Toronto: Eli Lilly Canada; 2012 Oct 16.

15. Nutropin: somatropin for injection, lyophilized powder for injection; 10 mg/vial. Nutropin AQ: somatropin injection, solution; 10 mg/2 mL vial. Nutropin AQ Pen, cartridge, somatropin injection, solution; 10 mg/2 mL pen cartridge. Nutropin AQ NuSpin: somatropin injection, solution; NuSpin injection device prefilled with cartridge: Nutropin AQ NuSpin 5 (5 mg/2 mL). Nutropin AQ NuSpin 10 (10 mg/2 mL). Nutropin AQ NuSpin 20 (20 mg/2 mL) [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2012 Dec 21.

16. Saizen: somatropin for injection. Lyophilized powder for reconstitution: 1.33 mg/vial, 3.33 mg/vial, 5 mg/vial, 8.8 mg/vial. Saizen click.easy: somatropin for injection. Lyophilized powder for reconstitution: 8.8 mg (8.0 mg/mL), 8.8 mg (5.83 mg/mL), 4 mg (1.5 mg/mL). Saizen: somatropin. Solution for injection in a cartridge: 6 mg (5.83 mg/mL), 12 mg (8 mg/mL). 20 mg (8 mg/mL) [product monograph]. Mississauga (ON): EMD Serono, A Division of EMD Inc., Canada; 2012 Aug 22.

17. Norditropin SimpleXx: somatropin solution for injection, cartridge: 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL. Norditropin NordiFlex: somatropin solution for injection pre-filled disposable pen: 5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL [product monograph]. Mississauga (ON): Novo Nordisk Canada Inc.; 2012 Sep 14.

18. Omnitrope: somatropin (rDNA origin) for injection. Lyophilized powder for injection: 5.8 mg/vial. Solution for injection: 5 mg/1.5 mL, 10 mg/1.5 mL [product monograph]. Boucherville (QC): Sandoz Canada Inc.; 2013 Jun 12.

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